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REAGENTS AND SYNTHETIC METHODS 30. PRACTICAL AND IMPROVED METHOD FOR FORMYLATING AMINO COMPOUNDS BY MEANS OF FORMIC ACID-DIMETHYLFORMAMIDE SYSTEM.

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ABSTRACT: Several amino compounds were formylated in high yields by means of formic acid-dimethylformamide, specially D,L-amino acids. The influence of this solvent was also briefly discussed.

Many methods have been developed for the formylating of amino compounds[1,2,3]. Formamide[4] alone serves to formylate some aniline derivates; esters of formic acid[5,6] gave good results in the formylation procedures, but sealed tubes or autoclaves are often required[7]. On the other hand, trichloroacetaldehyde[8-10] reacts with some amines to furnish the formamido compounds, but also gives addition products. Acetic formic anhydride[11-16] is a useful formylating agent, although sometimes acetylation occurs as it does formylation. Formic acid formylates varied ami

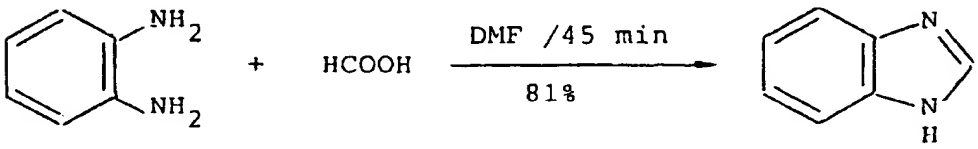
ne compounds; however, the formyl derivate is obtained upon reflux with a large excess of formic acid and for this, removal of water by azeotropic distillation is necessary. N-formylation of amines has also been achieved by using formic acid in the presence of carbodiimides[17], such as dicyclohexylcarbodiimide[18], but this method leads to difficulties in the separation of reaction products from undesired dicyclohexylurea. Dimethylformamide[19] has been used for formylating several amines, but prolonged periods (15-144 h) of heating were required. Finally, N,N-diformylacetamide[3] can also be used for N-formylation in good yields, even if the reagent is only obtained in poor yield (17%). Other methods can be used under mild reaction conditions[20], however the reagents are expensive and/or not readly avilables.

In order to overcome these drawbacks, we have found a simplified general way to convert amino compounds into the corresponding formyl derivates in excellent yields by simply refluxing in dimethylformamide a solution of the amine and formic acid in nearly equivalent amounts. In many cases, pure products are obtained by the work-up of the reaction mixture, without further purification.

$$R\text{-}NH_2 \xrightarrow[-H_2O]{DMF\ /\ HCOOH} R\text{-}NH\text{-}\overset{\overset{O}{\|}}{C}\text{-}H$$

The method is particularly interesting for a high-yield preparation of N-formylamino acids (Table 1) which are important starting materials for peptide[15] and Δ^2-oxazolone[21] synthesis.

Furthermore, when the reaction is carried out with o-phenylendiamine the cyclization happens within a brief time and the benzimidazole ring is obtained with a similar yield to the conventional method[22].



The importance of the dimethylformamide as a solvent can be noted in Table 2; in this order we have found that formylation of aminoacetic acid under different conditions is very much less effective than the method here described, wich is more suitable for a large preparative scale. The scope of the method is limited by the low nucleophilicity of some weackly basic amines such as 4-nitroaniline. Neither the phthalimide affords the corresponding formyl derivate.

The method described here is quite simple and the reagents used are readily available and inexpensive.

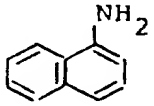
EXPERIMENTAL

Formylation of amino compounds with formic acid in N,N-dimethylformamide. General procedure.

A mixture of formic acid (1.92 ml, 51 mmol), N,N--dimethylformamide (15 ml) and the corresponding amino compound (30 mmol) was heated to reflux with good stirring until the amino compound can not longer be detected (10-120 min) by

TABLE 1

Formilation of amino compounds with formic acid in N,N--dimethylformamide as solvent.

Entry	Compound	t (min)	Yield (%)	m.p.°C (solvent)
1	$C_6H_5-CH_2-NH_2$	20	61	60-61 (H_2O)
2		120	73	136 (CCl_4)
3	$HOOC-CH_2-NH_2$	20	97	150-152 ($C_6H_5CH_3$)
4	$HOOC-\underset{\displaystyle CH_3}{\underset{|}{CH}}-NH_2$	35	91	146-147 ($C_6H_5CH_3$)
5	$HOOC-\underset{\displaystyle CH(CH_3)_2}{\underset{|}{CH}}-NH_2$	20	86	136-140 ($C_6H_5CH_3$)
6	$HOOC-\underset{\displaystyle CH_2-\emptyset}{\underset{|}{CH}}-NH_2$	10	81	168-169 ($C_6H_5CH_3$)
7	$HOOC-\underset{\displaystyle CH_2CH_2SCH_3}{\underset{|}{CH}}-NH_2$	15	94	89-91 ($C_6H_5CH_3$)
8	$HOOC-\underset{\displaystyle CH_3CHCH_2CH_3}{\underset{|}{CH}}-NH_2$	15	80	116 ($C_6H_5CH_3$)

Appendix of Table 1.

Entry	^{1}H-N.M.R. δ ppm(DMSO $_{d-6}$)
1	4.27(d,1H,CH_2), 5.6-6.5(s_b,1H,NH), 7.06(s,5H,arom.), 7.91(s,1H,COOH).
2	7.52(m,7H,arom.), 8.37(s,1H,NH), 8.54(s,1H,COH).
3	3.72(d,2H,CH_2), 7.75(d,1H,NH), 7.81(s,1H,COH), 9.50(s,1H,COOH).
4	1.32(d,3H,CH_3),4.25(m,1H,CH), 7.42(s,1H, COH), 7.91(d,1H,NH), 9.97(s,1H,COOH).
5	1.20(d,6H,CH_3), 2.44(sep,1H,C<u>H</u>-CH_3), 4.51 (m,1H,C<u>H</u>-COOH), 8.18(d,1H,NH), 8.22(s,1H, COH), 9.79(s,1H,COOH).
6	2.41(m,2H,CH_2), 4.10(m,1H,CH), 6.92(s,5H, arom.), 7.39(s,1H,COH), 7.83(d,1H,NH), 8.3-9.1(s_b,1H,COOH).
7	1.81(t,2H,C<u>H</u>$_2$-CH), 1.94(s,3H,CH_3), 2.30(t, 2H,C<u>H</u>$_2$-S), 4.15(m,1H,CH), 7.67(s,1H,COH), 7.84(s,1H,NH), 8.26(s,1H,COOH).
8	0.83(m,6H,CH_3), 1.52(m,2H,CH_2), 2.53(m,1H, C<u>H</u>-CH_3), 3.91(m,1H,C<u>H</u>-COOH), 7.47(s,1H,COH), 7.60(d,1H,NH), 8.52(s_b,1H,COOH).

TABLE 2

Formylation of aminoacetic acid (glycine) with formic acid under different conditions.

Solvent (ml)[a]	Cosolvent (ml)[a]	HCOOH (equiv)[b]	Dehydrating agent (g)[a]	T (°C)	time	Yield (%)
HCOOH (15)	———	excess	———	100	2h	63
HCOOH (15)	———	excess	——— [c]	100	4h	71
Toluene (10)	———	2.0	———	110	4h	67
Toluene (10)	DMF (5)	3.5	——— [c]	110	2h15m	60
Toluene (15)	DMF (5)	4.4	———	110	1h	69
Toluene (15)	DMF (5)	5.3	SiO_2 (1)[2]	110	2h	77
Toluene (15)	DMF (1.5)	1.7	SiO_2 (1.5)[2]	110	1h20m	68
DMF (15)	———	4.4	———	153	1h45m	95
DMF (15)	———	1.7	———	153	20m	97
DMF (15)	———	1.7	———	100	3h30m	25
AcOMe (15)	———	1.7	———	57	8h	3
Dioxane (15)	———	1.7	———	101	7h	32

a. Volume or weights refered to 30 mmol of glycine.
b. Equivalents of formic acid per mol of glycine.
c. Dean-Stark system was used for water separation.

T.L.C. analysis on silicagel plates using ethyl acetate as eluent (formylation of amino acids was monitored by dissolution of the starting material in the reaction mixture). Evaporation of the solvent and recrystallisation from toluene (10 ml) give the expected N-formylamino compounds, wich were characterized by their I.R. and ^1H N.M.R. spectra.

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